Three-Component One-Pot Synthesis of α-Hydroxylamino Phosphonates using Ionic Liquids

J. S. Yadav,* B. V. S. Reddy, P. Sreedhar

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax: (+91)-40-27160512; e-mail: yadav@iict.ap.nic.in

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Abstract: α-Hydroxylamino phosphonates are synthesised in a one-pot operation by three-component coupling reactions of aldehydes, hydroxylamines and diethyl phosphite using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids under mild and neutral conditions. The recovered ionic liquids can be recycled for four to five runs without loss of activity.

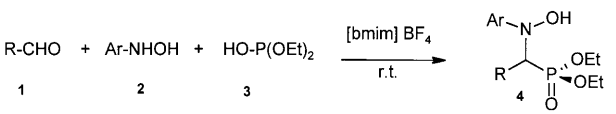
Keywords: α-hydroxylamino phosphonates; ionic liquids (ILs); nitrones

α-Aminoalkanephosphonates are an important class of biologically active compounds and their synthesis has received considerable current interest because of their structural similarity to α-amino acids.[1] They exhibit a wide spectrum of biological activities such as peptide mimetics,[2] enzyme inhibitors,[3] herbicides,[4] fungicides or plant growth regulators[5] and potent antibiotics[6] and also they act as inhibitors of HIV protease, PTPases and EPSP synthase.[7] Because of their fascinating biological properties, many procedures for the synthesis of α-amino phosphonates have been reported.[8,9] Among these methods, the nucleophilic addition of dialkyl phosphites to imines in the presence of acid catalysts is one of the most general and straightforward methods for the synthesis of α-amino phosphonates. However, many of these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and diethyl phosphite, because the amines and water that exist during the imine formation can decompose or deactivate the Lewis acids.[8] In order to avoid the problems associated with these methods, recently one-pot procedures have been developed for this conversion.[10] Although a large number of methods is available for the synthesis of α-amino phosphonates, only few methods are reported for α-hydroxylamino phosphonates.[11] Furthermore, there are no examples on the use of ionic liquids as promoters for three-component coupling reactions of aldehydes, hydroxylamines and diethyl phosphite to produce α-hydroxylamino phosphonates.

Room temperature ionic liquids are attracting growing interest as alternative reaction media for various chemical and biochemical transformations.[12] Accordingly, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, and immiscibility with a number of organic solvents, negligible vapour pressure and recyclability. Moreover, ionic liquids are simple and easy to recycle and their properties can be fine-tuned by changing the anion or the alkyl group attached to cation. These structural variations offer flexibility to the chemist to devise the most idealised solvent, catering for the needs of any particular process. Furthermore, ionic liquids have proved to be useful for the immobilisation of transition metal based catalysts, Lewis acids and enzymes.[13] As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis. Because of the great potential of room temperature ionic liquids as environmentally benign reaction media for catalytic processes, much attention has been currently focused on organic reactions promoted by ionic liquids.[13]

Here we report the use of ionic liquids as novel promoters for the synthesis of α-hydroxylamino phosphonates under mild conditions (Scheme 1, Table 1).

The treatment of benzaldehyde and phenylhydroxylamine with diethyl phosphite in 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid afforded the corresponding α-hydroxylamino phosphonate in 92% yield. In a similar fashion, various aldehydes and arylhydroxylamines reacted smoothly with diethyl phosphite to give the corresponding α-hydroxylamino phosphonates in excellent yields (see Experimental Section). The reactions proceeded efficiently at ambient temperature with high selectivity. No trace amounts of



Scheme 1.

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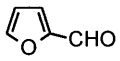
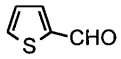
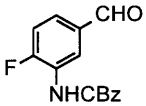
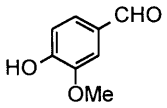
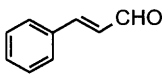
Table 1. Synthesis of α-hydroxylamino phosphonates using ionic liquids.[a]

Entry	Aldehyde	Hydroxylamine	[bmim]BF_4		[bmim]PF_6	
			Time [h]	Yield [%][b]	Time [h]	Yield [%][b]
a)	C_6H_5CHO	C_6H_5NHOH	2.5	92	3.5	89
b)	4-FC_6H_4CHO	C_6H_5NHOH	3.5	90	4.0	85
c)	C_6H_5CHO	4-MeC_6H_4NHOH	3.0	93	4.5	90
d)	4-$MeOC_6H_4CHO$	C_6H_5NHOH	3.5	90	4.0	87
e)	C_6H_5CHO	4-ClC_6H_4NHOH	3.0	89	5.0	85
f)	4-$NO_2C_6H_4CHO$	C_6H_5NHOH	4.0	87	5.5	80
g)	3,4,5-$(MeO)_3C_6H_2CHO$	C_6H_5NHOH	4.5	90	5.0	85
h)	C_6H_5CHO	4-BrC_6H_4NHOH	3.0	85	4.5	82
i)	4-Ph-C_6H_4CHO	C_6H_5NHOH	2.5	92	3.5	87
j)		C_6H_5NHOH	3.0	95	4.0	89
k)		C_6H_5NHOH	3.5	92	4.5	90
l)		C_6H_5NHOH	5.0	87	6.0	85
m)		C_6H_5NHOH	4.0	90	5.0	87
n)		C_6H_5NHOH	3.0	89	4.5	85

[a] All products were characterized by ^1H NMR, IR and mass spectra.
[b] Isolated and unoptimized yields after purification.

α-hydroxy phosphonates are obtained as a result of the reaction between the aldehyde and diethyl phosphite under these reaction conditions. However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time. The reactions in polar organic solvents such as DMF, DMSO and *N*-methylpyrrolidine did not proceed even under heating conditions (75–80 °C). Several aromatic, α,β-unsaturated, heterocyclic and aliphatic aldehydes reacted well with arylhydroxylamines and diethyl phosphite in ionic liquids to produce the α-hydroxylamino phosphonates. All the products were characterised by ^1H NMR, IR, and

mass spectroscopy. The reactions of various aldehydes, hydroxylamines and diethyl phosphite were examined in hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids. Among these ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) was found to be superior in terms of yields and reaction rates. The advantage of the use of ionic liquids as novel reaction medium for this transformation is that these ionic solvents could be easily recovered and reused in further runs. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and reused in subsequent reactions without further purification. Although the products obtained are of the same purity as in the first run, the yields gradual decreased in runs carried out using recycled ionic liquid. For example, the reaction of benzaldehyde, phenylhydroxylamine and diethyl phosphite afforded the corresponding α-hydroxylamino phosphonate in 92%, 85%, 82%, and 80% yields over four cycles. However, the activity of ionic liquid was consistent in runs and no decrease in yield was obtained when the recycled ionic liquid was activated at 80 °C under vacuum in each cycle. Thus, this method is advantageous over the acid-catalysed synthesis of α-hydroxylamino phosphonates.

In summary, this paper describes the three-component coupling reactions of aldehydes, hydroxylamines and diethyl phosphite to produce α-hydroxylamino phosphonates using ionic liquids as novel promoters. The simple operation combined with easy recovery and reuse of this novel reaction media makes this a more convenient, economic and user-friendly process for the synthesis of α-amino phosphonates of biological and medicinal importance. The use of ionic liquids as reaction media for this transformation allows one to avoid the use of moisture-sensitive and heavy-metal Lewis acids.

Experimental Section

General Procedure

Aldehyde (2 mmol), hydroxylamine (2 mmol), and diethyl phosphite (2 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL) were stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated under vacuum and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate: *n*-hexane (2:8) to afford pure α-hydroxylamino phosphonate. The rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs.

Representative Spectroscopic Data

4a: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 3.60 – 3.65 (m, 1H), 3.85 – 3.90 (m, 1H), 4.05 – 4.18 (m, 2H), 4.60 (d, 1H, *J* = 23.0 Hz), 4.80 (brs, OH), 6.58 (d, 2H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 7.8 Hz), 7.05 – 7.15 (m, 2H), 7.25 – 7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled): δ = 15.7, 15.8, 59.8, 61.2, 61.3, 115.9, 120.9, 127.4, 127.7, 129.3, 129.7, 132.1, 146.3; FAB-MS: *m/z* = 335 (M^+), 319, 182, 104, 77, 51; IR (KBr): ν = 3304, 2924, 1602, 1500, 1237, 1024, 966, 750, 696 cm^{-1}.

4 g: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 6.7 Hz, 3H), 1.25 (t, *J* = 6.7 Hz, 3H), 3.60 – 3.65 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 3.85 – 3.90 (m, 1H), 4.05 – 4.15 (m, 2H), 4.60 (d, 1H, *J* = 23.0 Hz), 4.70 (brs, OH), 6.58 (d, 2H, *J* = 8.0 Hz), 6.60 – 6.70 (m, 3H), 7.05 (t, 2H, *J* = 7.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled): δ = 16.2, 16.4, 55.3, 56.6, 57.3, 60.8, 63.4, 63.5, 106.6, 113.9, 118.5, 129.2, 131.4, 137.7, 146.3, 153.3; FAB-MS: *m/z* = 425 (M^+), 409, 318, 272, 242, 180, 153, 106, 64, 45; IR (KBr): ν = 3306, 2928, 1605, 1504, 1249, 1176, 1023, 969, 837, 749 cm^{-1}.

4j: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H), 3.95 – 4.20 (m, 4H), 5.0 (d, 1H, *J* = 24.0 Hz), 6.20 (s, 1H) 6.45 (s, 1H), 6.80 (t, 1H, *J* = 7.9 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 7.25 (s, 1H), 8.25 (brs, OH); ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled): δ = 16.0, 16.3, 53.8, 63.2, 63.3, 104.2, 110.7, 113.9 119.9, 129.0, 137.0, 144.1, 146.1; FAB-MS: *m/z* = 325 (M^+), 309, 263, 217, 187, 171, 136, 97, 75, 64, 45; IR (KBr): ν = 3308, 2926, 1602, 1497, 1235, 1025, 967, 750 cm^{-1}.

4l: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H), 3.70 – 3.80 (m, 1H), 3.85 – 3.90 (m, 1H), 4.05 – 4.15 (m, 2H), 4.65 (d, 1H, *J* = 23.0 Hz), 5.15 (s, 2H), 6.60 (d, 2H, *J* = 8.0 Hz), 6.90 – 7.15 (m, 5H), 7.25 – 7.40 (m, 6H), 8.25 (brs, OH); ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled): δ = 16.3, 16.5, 57.1, 63.4, 63.5, 67.3, 114.8, 118.5 119.8, 122.5, 126.2, 128.3, 128.4, 128.6, 129.1, 129.8, 132.4, 134.1, 145.9, 149.1, 152.7; FAB-MS: *m/z* = 502 (M^+), 393, 349, 241, 213, 111, 92, 64, 48; IR (KBr): ν = 3409, 3305, 2927, 1710, 1602, 1503, 1234, 1023, 970, 749 cm^{-1}.

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